Effect of adductor canal block on pain in patients with severe pain after total knee arthroplasty: a randomized study with individual patient analysis

U. Grevstad1*, O. Mathiesen3, T. Lind2 and J. B. Dahl4

1 Department of Anaesthesia and Intensive Care Medicine and 2 Department of Orthopaedic Surgery, Copenhagen University Hospital, Gentofte Hospital, Niels Andersens Vej 65, 2900 Hellerup, Denmark
3 Section of Acute Pain Management and 4 Department of Anaesthesia, Centre of Head and Orthopaedics, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
* Corresponding author. E-mail: ulrik.grevstad@hotmail.com

Editor’s key points

- Effective postoperative analgesia is important after total knee arthroplasty as severe pain can impair mobilization.
- Adductor canal block was studied in patients with severe postoperative movement-related pain.
- With an effective block, there was a clinically significant reduction in pain scores on knee flexion.
- Further work is needed to establish the place of this block in clinical practice.

Background. Total knee arthroplasty (TKA) is associated with varying degrees of pain. A considerable proportion (25–40%) of patients experience severe pain, despite a comprehensive multimodal analgesic regimen. We hypothesized that adductor canal block (ACB) would reduce pain in this patient category compared with placebo.

Methods. Fifty patients with severe pain, defined as having a visual analogue scale (VAS) pain score of ≥60 during active flexion of the knee on the first or the second postoperative day after TKA, were included in this randomized, double-blind, placebo-controlled trial. All the patients had received a comprehensive multimodal analgesic regimen. Group A received an ACB with ropivacaine 0.75%, 30 ml at time 0 and isotonic saline after 45 min. Group B received an ACB with isotonic saline at time 0 and ropivacaine 0.75%, 30 ml after 45 min.

Results. A 32-mm difference in VAS pain score, during active flexion of the knee (primary endpoint), was observed in favour of Group A, 95% confidence interval (CI): 23–42, \( P < 0.0001 \). At rest, the difference in VAS pain score was 15 mm in favour of Group A, 95% CI: 8–23 mm, \( P = 0.0001 \). Individual patient analysis revealed that 25% of the patients had no effect during active flexion. At rest, however, only 8% had more than mild pain after ACB compared with 57% at inclusion.

Conclusions. ACB reduced VAS with 32 mm, during active flexion of the knee, in patients with severe pain after TKA, but a large proportion (78%) still had at least moderate, movement-related pain.


Keywords: acute pain; arthroplasty, replacement, knee; nerve block; pain, postoperative

Accepted for publication: 7 October 2013

Total knee arthroplasty (TKA) is a procedure often associated with intense postoperative pain, despite a comprehensive multimodal analgesic regimen.1

Epidural analgesia is an alternative. However, this procedure faces a relatively high failure rate2 3 and produces well-known side-effects such as urinary retention and motor block,4 the latter potentially hindering mobilization.

Femoral nerve block (FNB) is a well-established treatment for postoperative pain after TKA.5 FNB is, however, invariably followed by reduced quadriceps muscle strength6 7 and associated with the risk of falling.8 – 10

Adductor canal block (ACB) is a relatively new block with promising results reported in initial studies.11 12 Compared with FNB, ACB results in less reduction in the quadriceps muscle strength13 as only the motor nerve to the vastus medialis of the quadriceps muscle traverses the adductor canal. Injecting a large volume of ropivacaine in the adductor canal should, in theory, affect not only the two largest sensory contributors from the femoral nerve to the knee—the saphenous nerve and the branch to vastus medialis—but also the terminal end of the posterior branch of the obturator nerve as it enters the distal part of the adductor canal.

The aim of this study was to evaluate the effect of ACB on pain during active flexion of the knee (primary outcome) and at rest (secondary outcome), in patients with severe pain after TKA, compared with placebo, and to evaluate the effect of the block in individual patients. Our definition of severe pain is a visual analogue scale (VAS) score of ≥60 mm out of
100 mm during an active 45° knee flexion, despite a comprehensive multimodal analgesic regimen.

Methods
The study was approved by the Danish Medicines Agency (EudraCT nr.2011-005368-5), the local Regional Ethics Committee (H-4-2011-154), and the Danish Data Protection Agency and registered at ClinicalTrials.gov (NCT01549704). The Copenhagen University Hospital Good Clinical Practice Unit monitored the trial. The study was carried out in accordance with the principles of the Helsinki declaration and data are presented in accordance with the CONSORT statement.14 From January 2012 to November 2012, patients who were about to undergo elective, unilateral, primary TKA at Copenhagen University Hospital, Gentofte Hospital, Denmark, attended a full-day seminar ~1 week before surgery. At this seminar, besides being informed about the surgery, anaesthesia, and what to expect regarding the perioperative period, they were informed about the study—both in plenum and during the following individual contact with an anaesthesiologist. The information about the study was given in accordance with recommendations and requirements from the local Regional Ethics Committee. Patients were screened on the first or the second post-surgical day for inclusion in the study. Written informed consent was obtained from all the subjects before enrolment. The primary investigator, who also performed all the blocks and assessments, did the screening and enrolment.

The inclusion criteria were: unilateral TKA and a VAS pain score of >60 mm during an active 45° flexion of the knee on the first or second postoperative day, age 30–85 yr, ASA classification I–III, and BMI 18–40 kg m⁻². The exclusion criteria were: inability to cooperate, inability to understand or speak Danish, allergy to ropivacaine, and medicine or alcohol abuse.

Surgery, anaesthesia, and postoperative analgesia
TKA was performed by one of four different surgeons with insertion of tricompartmental prostheses using a standard medial parapatellar approach. Cruciate-substituting and cruciate-retaining designs were used. Surgery was performed in a bloodless field using a femoral tourniquet (100 mm above systolic arterial pressure). At the end of the surgery, a compression bandage from the toes to the mid-thigh was applied. Surgery was performed under spinal anaesthesia with 10–15 mg bupivacaine 0.5% or under general anaesthesia with propofol and remifentanil.

All the patients had received a standardized multimodal analgesic regimen (unless contraindicated): (i) Before operation—oral celecoxib 400 mg, acetaminophen 1 g, and gabapentin 600 mg; (ii) Intraoperatively—local infiltration analgesic regimen (unless contraindicated): (i) Before operation with propofol and remifentanil. Surgery was performed under spinal anaesthesia, with 10–15 mg bupivacaine 0.5% or under general anaesthesia with propofol and remifentanil.

A 15-mm reduction in VAS in Group A compared with Group B, difference in VAS pain score between Group A and Group B, during an active 45° flexion of the knee at t45.

Secondary outcomes were differences in VAS pain scores between the groups at different time points both at rest and during flexion of the knee.

VAS pain scores were assessed at baseline and 15, 30, 45, 60, 75, and 90 min hereafter. VAS scores at rest were assessed before VAS scores during flexion.

The success rate of the block was assessed by testing for sensation of cold in the saphenous area of the lower leg before the first block and at the end of the study period.

Statistical analysis
A 15-mm reduction in VAS in Group A compared with Group B, during an active 45° flexion of the knee, 45 min after the first block was considered clinically relevant. We estimated a standard deviation (SD) of 15 from a previous study at our institution. With a =0.05 and a power of 90%, 2 × 22 patients would be required. To account for the uncertainty in predicting the actual SD, 2 × 25 patients were included. The data were analysed using IBM SPSS Statistics version 20.
The data were analysed using a linear mixed model. Treatment, time, and the interaction treatment × time were included in the model. The model has time as a repeated effect with a first-order autoregressive covariance structure (AR[1]). Baseline values were included as a covariate to compensate for baseline differences. The data are presented as the mean difference between the groups, at different times, with a 95% confidence interval (95% CI) for the difference. The values are based on estimated marginal means.

Since the mixed model is not yet widely used, the primary endpoint is also presented using non-parametric statistics (independent samples Hodges–Lehman median difference in VAS pain score during an active 45° flexion at 45 min between the groups with a 95% CI). P-values were corrected with the Bonferroni test for repeated measurements (see, however, the Results section).

In addition to the above analyses, we calculated numbers needed to treat (NNT), defined as the number of patients who must receive a block for one patient to experience a decrease in VAS pain score of >50%, during active flexion of the knee and at rest. Further, the proportion of patients with more than ‘mild pain’ (VAS > 30) during active flexion of the knee and at rest before and after treatment was calculated.16 17

Data handling
After inclusion of the last patient, all the data were entered into a spreadsheet and checked for typos by two investigators. The pharmacy that performed the randomization, delivered a list, assigning each patient to one of the two primary groups (‘y’ and ‘z’) without revealing the identity of the groups. After data analysis was completed and conclusions were drawn, the pharmacy reported which of the primary groups ‘y’ and ‘z’ corresponded to Group A and Group B.

Results
Of 193 patients assessed for eligibility, 50 were included and randomized. One patient completed the trial but was excluded as it became apparent that she did not understand the VAS measurements. She was excluded before knowledge of which of the primary groups she belonged to. One patient was in extreme pain and was given i.v. fentanyl after t75, and values obtained before this are included in the analysis. Thus, data from 49 patients were analysed for the primary endpoint (Fig. 1). The groups were similar with respect to patient characteristics and perioperative data (Table 1).

Comparisons at multiple time points are usually corrected to reduce the risk of a type I error, but can create other problems due to the within-group correlation. Ignoring these correlations leads to unnecessary conservative results. Another concern is the design of the study—correcting the comparisons after the second block actually supports our hypothesis that the difference would disappear after the second block. Consequently, we have chosen to present two rows of P-values, uncorrected and Bonferroni corrected for 11 comparisons.

Pain during a 45° knee flexion
At 45 min after the first block (t45), there was a 32-mm difference in VAS pain score, during an active 45° flexion of the knee (primary endpoint), in favour of Group A compared with Group B (95% CI: 23–42), P = 0.0001. When analysed using non-parametric statistics, similar results were found: an estimated difference of 31 mm (95% CI: 21–43), P < 0.0001.

At the end of the study (t90), the difference was negligible: 3 mm (95% CI: –6 to 13), P = 0.47 (Fig. 2). See Table 2 for pairwise comparisons between the groups at different time points and Figure 3a and c for individual line plots.

NNT for pain during active flexion of the knee is 3.4 (95% CI: 2.1–9.1); the ratios are 7/24 in Group A vs 0/25 in Group B at 45 min. Per protocol, all the patients had a VAS score of >30 during active flexion of the knee at baseline. Thirty-eight out of 49 patients had a VAS score of >30 during active flexion of the knee at the end of the study, equal to a proportion of 78% (95% CI: 66–89%).

Pain at rest
At 45 min after the first block, there was a 15-mm difference in VAS pain score at rest in favour of Group A compared with Group B (95% CI: 8–23 mm), P = 0.0001 (Fig. 4). At the end of the study, the difference was no longer apparent. See Table 3 for pairwise comparisons between the groups at different time points and Figure 3b and d for individual line plots.

The NNT for pain at rest is 2.1 (95% CI: 1.4–4.4); the ratios are 19/24 in Group A vs 8/25 in Group B at 45 min. At baseline, 28 out of 49 patients had a VAS score of >30 at rest, equal to a proportion of 57% (95% CI: 43–71). Four out of 49 patients had a VAS score of >30 at the end of the study, equal to a proportion of 8% (95% CI: 0–16).

Analysis of individual patients
In Group A, seven out of 24 patients (id 5, 12, 17, 19, 23, 28, 34) had no (defined as less than our pre-specified minimal relevant difference of a 15-mm reduction in movement-related pain) effect of the block at t45, equal to a proportion of 29% (95% CI: 15–49) (Fig. 3a).

In Group B, five out of 25 patients (id 7, 10, 11, 14, 30) had no effect of the block at t90, equal to a proportion of 20% (95% CI: 9–39) (Fig. 3c).

For both groups, the overall ‘non responder’ rate was 25% (95% CI: 15–38).

Block success rate
All patients but three were tested for the ability to sense cold in the saphenous area before the first block. One patient (id 50, Group A) did not have any sensation in this area and could therefore not be included in the evaluation of block success rate. The block success rate, assessed as the loss of sensation of cold at the end of the study period, was 98% (44/45).
Discussion

The aim of this study was to evaluate the analgesic effect of the ACB in patients with inadequate, movement-related pain relief despite a comprehensive multimodal analgesic regimen.

Table 1 shows that Group A and Group B had received the equivalence of 90 vs 103 mg oral morphine after operation and that they still had a baseline VAS score during flexion of the knee of 81 vs 78 mm. It is reasonable to conclude that the patients included in the present study could not be treated with conventional pain medication and the finding of a reduction in VAS pain of 32 mm between the groups at t45 (primary endpoint) demonstrates that the block is an acceptable alternative when dealing with patients suffering severe, movement-related pain. This finding is supported by the fact that Group B experienced a comparable decrease in VAS pain when they received the active block (Fig. 2 and Table 2).

When designing the study, the authors agreed that a reduction of 15 mm in movement-related VAS score was to be considered clinically relevant. This is controversial and the literature is not clear about this issue, in particular not in patients with extensive pain already receiving a comprehensive multimodal analgesic regimen. Several studies have examined what patients in acute pain regard as a minimal clinical relevant difference—they find that a reduction of 9–13 mm in VAS pain score is being perceived as relevant by the patients. In the study by Kelly, the minimal relevant difference was independent of the severity of pain being experienced. In a reanalysis of two clinical trials of postoperative pain, one concerning unilateral knee arthroplasty, these numbers were reproduced.

In recent reviews, it has been suggested that ‘no worse than mild pain’ (VAS < 30 mm) should be considered as a simple, universal outcome and that any outcome worse than mild pain should be regarded as a mark of analgesic failure—however,
It has also been emphasized, though, that ‘no single drug will treat successfully more than a minority of patients with a painful condition’.17

In the light of these reviews, it is important not to overstate the results of the present study, since a large proportion of the patients (78%) still suffered at least moderate movement-related pain (VAS > 30) after the active block. In contrast, the proportion of patients with more than mild pain at rest (VAS > 30) decreased from 57% at baseline to 8% after both groups received active treatment.

We found a relatively high proportion of ‘non responders’. Of these, Patients 5, 17, 19, 23, and 28 reported that pain in the anterior part of the knee had disappeared and complained of pain only in the posterior part of the knee after the study period. Patient 7 had no pain in the knee after the study period, but only in the thigh, and Patient 12 had unsuccessful block. Thus, defining these patients as ‘non responders’ may be considered rather conservative. A possible explanation is that the pain perceived by these patients originated from nerves not traversing the adductor canal, most likely from the ischiadicus nerve.
Jæger and colleagues examined the effect of ACB on established pain in the early postoperative period after TKA compared with placebo. They found no significant difference in VAS pain scores during active flexion of the knee at their primary endpoint 1 h after operation or at rest, but a significant reduction in VAS during active flexion of the knee in favour of ACB, when calculated as the area under the curve for the study period 1–6 h after operation. There were though logistic difficulties resulting in 25% of the patients not receiving the study medication as planned at 0.5 h after the last suture—perhaps not leaving enough time for the block to reach the maximum effect at the primary endpoint.

Jenstrup and colleagues compared the effect of repeated ACB boluses, through a catheter, with those of placebo. They found a significant reduction in morphine consumption during the study period (0–24 h), a significant reduction in pain scores during an active 45° flexion of the knee, and a reduction in time used to perform a mobilization test. In a recently published study, Andersen and colleagues examined the effect of ACB in 40 TKA patients receiving a basic analgesic regimen with that of LIA, and demonstrated a significant effect of the block.

The effects demonstrated in the present study are rather pronounced compared with observations in earlier studies. It should be noted that the patient population in the current study differs from those in previous studies. Thus, patients were assessed and included 24–48 h after the surgical procedure and only patients with severe...
movement-related pain were included, which may explain the different results. Unfortunately, we are not aware of similar data with other techniques such as LIA, FNB, or epidurals, in patients with established, severe, movement-related pain. Most often, such analgesic measures are initiated before operation or intraoperatively, without knowing how severe the pain will be in the postoperative period. Consequently, these studies have included patients who will experience low, moderate, and severe pain, making a direct comparison difficult.

The use of the rather large volume of 30 ml for the ACB in the present study is controversial. Some would argue that the analgesic benefit could be due to a spread of the local anaesthetic in the adductor canal to the femoral nerve and that we just evaluated the well-known effect of an FNB. We find this unlikely since the same volume recently was demonstrated to result in only a minimal reduction in quadriceps muscle strength, compared with the FNB.13 We deliberately chose this volume as we regard ACB as a ‘high volume block’.

In Figure 3c, no placebo effect is observed. A possible explanation for this could be that the patients knew that they would receive both a placebo and an active ACB, if they had high expectations and felt no profound difference, they could guess that they had the placebo block. Another explanation could be a possible ceiling effect due to the high baseline scores, obscuring a possible placebo effect. This could explain why we see a placebo effect at rest, where the baseline scores were much lower (Fig. 3c).

The study was not powered to evaluate any safety aspects. One patient (id 37, Group B) still had loss of sensation in the saphenous area of the blocked leg 3 months after the block, and suffered from a fall on the ward 10 h after the active block (no complications to the fall). Before surgery, the patient was diagnosed with protrusions of the 4th and 5th lumbar disc (MR-spine verified), with partial loss of sensation and reduced muscle strength in the operated leg. Whether the fall was related to the block cannot be ruled out, neither can the possibility that we caused an injury to the saphenous nerve.

From the sparse material published about follow-up of the ACB,22,23 it is difficult to say anything about the incidence of nerve injuries. The incidence will most likely be comparable with what is seen with other nerve blocks.24–28 In the case of a nerve injury, ACB, however, has the ‘advantage’ of being a mainly sensory block with less detrimental consequences.

Our study has several limitations. We assessed only pain during rest and active flexion of the knee—it would have been interesting to evaluate the effect on motor strength and ambulation. Further, we only evaluated the immediate effect of the block on pain and we did not evaluate an extra-regional control site for pain stimulation; therefore, a potential systemic effect of ropivacaine cannot be excluded. Having a BMI of >40 as an exclusion criterion also makes the study less inferential.

Future studies should address whether the analgesic effect demonstrated in the present study is comparable with the effect observed with FNB, and should examine the effect of ACB on motor strength and mobilization in patients undergoing TKA. Further, optimal volumes, concentrations, and administrations (single shot vs continuous infusion) should be investigated.

In conclusion, ACB is a promising option when used as a rescue analgesic technique for patients in severe pain after TKA. A mean VAS reduction of 32 mm during active flexion of the knee, and a relatively low NNT = 3.4 for movement-related pain was demonstrated favouring the ACB. At rest, the NNT was 2.1 and the proportion of patients experiencing more than mild pain (VAS > 30) decreased from 57% to 8%. However, ~25% of
the patients had no effect from the block and a large proportion (78%) still had at least moderate movement-related pain. Supplementary treatment modalities must be sought for these patients.

Authors’ contributions
U.G.: study conception and design, patient recruitment, data collection, data analysis, and writing up the first draft and the final paper. O.M.: study conception and design, data analysis, revision of drafts, and final approval. T.L.: study design, data analysis, revision of drafts, and final approval. J.B.D.: study conception and design, data analysis, revision drafts, and final approval.

Acknowledgements
The authors thank the entire staff in the Department of Anaesthesia (especially the nurses in the perioperative section) and the Department of Orthopaedics (especially the nurses and the porters of ward 1601) at Copenhagen University Hospital, Gentofte, Denmark.

Declaration of interest
None declared.

Funding
All expenses were covered by departmental sources.

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Handling editor: L. Colvin